Effect of Bevacizumab Nasal Spray on Epistaxis Duration in Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial

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BACKGROUND  Epistaxis is the most frequent and disabling manifestation of hereditary hemorrhagic telangiectasia (HHT). The efficacy of intravenous bevacizumab (an anti–vascular endothelial growth factor monoclonal antibody) for epistaxis has been shown. However, the efficacy of intranasal bevacizumab has yet to be evaluated.

OBJECTIVE  To evaluate the efficacy of 3 different doses of bevacizumab administered as a nasal spray in a repeated manner for the duration of nosebleeds in patients with HHT.

DESIGN, SETTING, AND PARTICIPANTS  Randomized, multicenter, placebo-controlled, phase 2/3 clinical trial with dose selection at an intermediate analysis and prespecified stopping rules (nonbinding stopping for futility). Patients aged 18 years or older with a diagnosis of HHT were recruited from 5 French centers from April 2014 to January 2015 with a 6-month follow-up after the end of treatment. Participants had a history of self-reported nosebleeds with a monthly duration of more than 20 minutes in at least the 3 months prior to inclusion corroborated by epistaxis grids completed during the same preinclusion period.

INTERVENTIONS  Eighty consecutive HHT patients were randomized and treated in the phase 2 study, with 4 parallel groups in a 1:1:1:1 ratio. One group received placebo (n = 21); the other 3 received bevacizumab nasal spray. Each bevacizumab group received a different dose of the drug (25 mg [n = 20], 50 mg [n = 20], or 75 mg [n = 19] per treatment) in 3 doses 14 days apart for a total treatment duration of 4 weeks, resulting in a total dose of 75 mg, 150 mg, and 225 mg in each treatment group.

MAIN OUTCOMES AND MEASURES  Mean monthly epistaxis duration for 3 consecutive months immediately after the end of the treatment.

RESULTS  Of the 80 patients who were randomized (mean age, 60.47 [SD, 10.61] years; 37 women [46.25%]), 75 completed the study. Mean monthly epistaxis duration measured at 3 months was not significantly different in the 59 patients receiving bevacizumab in comparison with the placebo group (P = .57) or between the bevacizumab groups. The mean monthly epistaxis duration was 259.2 minutes (95% CI, 82.1-436.3 minutes) in the 25-mg group, 244.0 minutes (95% CI, 81.8-406.2 minutes) in the 50-mg group, 215.0 minutes (95% CI, 102.8-327.2 minutes) in the 75-mg group, and 200.4 minutes (95% CI, 109.3-291.5 minutes) in the placebo group. Toxicity was low and no severe adverse events were reported. This study was terminated prior to phase 3 for treatment futility after interim analysis on the recommendations of an independent data monitoring committee.

CONCLUSIONS AND RELEVANCE  In patients with HHT, a bevacizumab nasal spray treatment of 3 administrations at 14-day intervals with doses of 25 mg, 50 mg, or 75 mg per spray, compared with a placebo, did not reduce monthly epistaxis duration in the 3 consecutive months immediately after the end of treatment.

TRIAL REGISTRATION  clinicaltrials.gov Identifier: NCT02106520


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Erected hemorrhagic telangiectasia (HHT) is a dominantly inherited genetic vascular disorder characterized by recurrent epistaxis, cutaneous telangiectasia, and visceral arteriovenous malformations. Diagnosis is based on clinical criteria.1

The most obvious expression of the disorder is the occurrence of spontaneous, repeated epistaxis.2 These epistaxis episodes can be severe and life threatening; they are often the cause of chronic anemia and can require treatment with iron supplementation and blood transfusions. There is currently no medical or surgical treatment available to cure the nosebleeds definitively. Repeated surgical treatments often lead to complications, such as nasal septum perforation, resulting in worsening of the nosebleeds.

Hereditary hemorrhagic telangiectasia is related to an imbalanced state between antiangiogenic factors and proangiogenic factors, such as vascular endothelial growth factor (VEGF),3 secondary to mutations in 3 genes, ENG (encoding endoglin),4 ACRLVI (encoding activin receptor-like kinase 1),5 and MADH4 (encoding SMAD4). Because of the molecular mechanisms involved, a small phase 2 clinical trial was conducted using intravenous bevacizumab (an anti-VEGF monoclonal antibody) in patients with severe hepatic forms of HHT. Significant improvements in liver consequences as well as epistaxis were reported.6 To limit the systemic adverse effects of bevacizumab and to make the treatment easier, local administration seemed suitable. Bevacizumab transport through porcine nasal mucosa was evaluated and evidence of absorption was observed.7 Furthermore, several published cases reported the potential efficacy of a bevacizumab nasal spray.8,12

A phase 1 study13 concluded that bevacizumab administered by nasal spray in HHT was safe regardless of dose. A phase 2 study was thus needed to assess the efficacy of a bevacizumab nasal spray on epistaxis in HHT. The present study reports the design of a combined phase 2/3 study to test the efficacy of a bevacizumab nasal spray and the results of the phase 2 study on the duration of nosebleeds vs placebo administered in a repeated manner in patients with HHT complicated by nosebleeds.

**Methods**

**Study Overview**

The study was a randomized, multicenter, placebo-controlled clinical trial. This study was approved by the local research ethics committee and by the French Medical Products Agency in February 2014. Written informed consent was obtained from all patients in accordance with national regulations. The trial was conducted in accordance with the principles of the Declaration of Helsinki14 and Good Clinical Practice guidelines.

**Patients**

This study enrolled patients aged 18 years or older with clinically confirmed HHT and a history of epistaxis (mean >20 minutes per month over a 3-month period prior to inclusion, assessed using nosebleed reporting grids filled in by the patients) who had not undergone nasal surgery in the 3 months prior to inclusion.

Exclusion criteria included women who were pregnant or those likely to become so during the study, patients with an ongoing infectious condition, patients who had participated in another clinical trial in the 28 days prior to inclusion, patients with known hypersensitivity to the active ingredients or one of the carrier agents, or patients who had incompletely filled in the nosebleed grids in the 3 months preceding inclusion. Potentially eligible patients were identified by physicians working in the French HHT network and informed of the study during a consultation in an HHT center.

**Key Points**

**Question** Are bevacizumab nasal sprays an efficient treatment for nosebleeds in patients with hereditary hemorrhagic telangiectasia (HHT) when 3 doses of 25 mg, 50 mg, or 75 mg are administered at 14-day intervals?

**Findings** In this randomized, combined phase 2/3 clinical trial among 80 patients, no significant difference was observed in mean monthly epistaxis duration after the end of treatment. This study was terminated early for treatment futility after the intermediate analysis.

**Meaning** In patients with HHT, a bevacizumab nasal spray treatment did not reduce monthly epistaxis duration 3 months after the end of treatment in comparison with a placebo.

**Study Design**

This was an adaptive combined phase 2/3 study with dose selection during the interim analysis.15,16 The first step consisted of a randomized study with 4 parallel groups in a 1:1:1:1 ratio (phase 2 study): 1 placebo group and 3 groups receiving different doses of bevacizumab (25, 50, or 75 mg per treatment) administered as a nasal spray (3 sprays 14 days apart for a total treatment duration of 4 weeks), resulting in total doses of 75 mg, 150 mg, and 225 mg in the bevacizumab treatment groups. An interim analysis was planned at the end of step 1, after inclusion and 3 months of follow-up of the 80 patients. Then, the most efficient dose would be selected and the second stage of the trial would begin, with the patients randomized into 2 groups, 1 receiving the bevacizumab dose retained and 1 receiving placebo, using an allocation ratio of 2:1 (phase 3 study). An independent data monitoring committee composed of a statistician, an ear, nose, and throat specialist, an HHT specialist, and a clinical pharmacologist evaluated data at the interim analysis. Nonbinding rules for termination of the study for futility on the recommendations of the independent data monitoring committee were designed to guarantee the greatest flexibility for the second stage.16 There were no prespecified thresholds for differences.

Data were collected at each treatment visit (days 0, 14, and 28) and during the 6-month follow-up (2 visits at 3 and 6 months after the end of treatment), including a physical examination, ear, nose, and throat examination, a questionnaire on nasal obstruction, measurement of hemoglobin and
ferritin levels, and assessment for adverse events, plus a telephone questionnaire 1 and 2 months after the end of treatment. All data were collected centrally at the clinical trials unit of the Hospices Civils de Lyon, France.

A pharmaceutical department (Lyon center) randomized allocation of the study drug doses or placebo. The randomization list was established using SAS software, version 9.2 (SAS Institute Inc), and was balanced per center with a block of 4 patients with 1 placebo patient for 3 study drug patients using a 1:1:1:1 allocation ratio. Patients received a 1-day treatment of bevacizumab or placebo intranasally 3 times, at 14-day intervals, for a total treatment duration of 4 weeks. Undiluted bevacizumab (25 mg/mL of bevacizumab, trehalose dihydrate, sodium phosphate, polysorbate 20, and water for injections [Roche]) was packaged by a pharmaceutical department in a calibrated nasal spray bottle that delivered 0.1 mL per nebulization. The solution was used as is and prepared on the day of administration to the patients by the hospital pharmacy (unblended) at the hospital center in which the patients were managed. Regardless of randomization group, to maintain blinding it was necessary to prepare 3 different yet physically identical spray bottles for each patient. The 3 spray bottles were prepared with either bevacizumab or placebo in relation to the randomization group and numbered so as to determine their order of administration. Each patient received 3 nasal nebulizations, administered every 30 minutes into each nostril over a 2-hour period in the course of a consultation with blood pressure measurement before and after treatment. The placebo used was 0.9% sodium chloride.

**Study End Points**

The primary outcome was mean monthly epistaxis duration assessed by monitoring epistaxis grids (Supplement 1) completed by patients for 3 months after the end of the treatment (from day 29 to day 118). These grids were compared with mean monthly epistaxis duration in the 3 consecutive months before the beginning of the treatment (from day –90 to day –1). The efficacy criterion was not measured immediately at the end of treatment because the previous study highlighted that efficacy was delayed compared with the beginning of treatment.

Secondary outcomes were mean monthly frequency (number per month) of nosebleeds, quality of life (evaluated with the 36-item Short Form Health Survey [SF-36] quality-of-life questionnaire), number of red blood cell transfusions, and biological efficacy criteria (hemoglobin and serum ferritin levels). Epistaxis grids and blood transfusions were recorded for the 3 months before treatment (from day –90 to day –1) and during the entire study and hemoglobin and ferritin levels were measured at days 0, 14, 28, 58, 118, and 208. The SF-36 quality-of-life questionnaire was administered at day 0, day 118 (3 months after the end of treatment), and day 208 (6 months after the end of treatment).

**Safety**

Safety was evaluated at each visit by physical examination (monitoring of blood pressure; clinical ear, nose, and throat examination to check the nasal septum, the absence of nasal perforation after treatment, and other adverse effects on nasal mucosa), laboratory testing, and assessment for adverse events. Adverse events were classified and recorded using the web-based MedDRA. Furthermore, based on known bevacizumab adverse events, any events were classified by the investigators as unrelated, doubtfully or possibly, or probably or certainly related to the treatment. The independent data monitoring committee met in case of the occurrence of serious adverse events.

**Statistical Analysis**

The sample size was first computed so that each test of the elementary null hypothesis $H_0$ would have a power close to $1 - \beta = .9$ to show a relative decrease of 40% in the mean epistaxis duration compared with placebo, which was judged to be a significant improvement for patients. Given the assumed log-normal distribution of the outcome and data in the literature, this would correspond to showing an absolute difference in the means of the logarithms of the mean epistaxis duration of $\delta = -0.52$ compared with placebo. It was assumed that the standard deviation of the logarithm of mean epistaxis duration was $\sigma = 0.63$ in each group. An overall number of patients of 40 per group ensured a power of 89%. With a 1:2 allocation ratio at the second stage, selecting $n_1 = n_2 = 20$ without interim analysis provides an overall power of 94.4%, more than 90%. However, it was decided to keep this number of patients to account for the power loss induced by the use of the Fisher combination test and to maintain better power in case bevacizumab was slightly less effective than expected or if the standard deviation of the outcome was slightly higher than planned.

It was decided to perform the interim analysis when 20 patients per group had been randomized. The interim analysis with dose selection and reassessment of the sample size for the second stage was prespecified and carried out by an independent statistician who was blinded to the study groups (except the placebo group).

Quantitative parameters at inclusion were presented as means and standard deviations and medians and ranges for all groups and were compared using the $t$ test (or Mann-Whitney test in the case of nonnormality). Qualitative parameters at inclusion were presented as numbers and percentages and compared using the $\chi^2$ test (or Fisher exact test when conditions for the $\chi^2$ test were not fulfilled). The efficacy and safety population was defined as all treated patients. Patients were analyzed in the treatment group to which they were randomized (intention-to-treat analysis). Concerning the main outcome, the logarithms of the mean duration of nosebleeds were analyzed with a $t$ test with Simes correction for multiplicity.

Differences between monthly mean number and duration of epistaxis episodes before and after treatment were compared between the placebo and bevacizumab groups with an analysis-of-variance test (or Kruskal-Wallis test in the case of nonnormality). Trends over time for hemoglobin and ferritin levels and all dimensions of the SF-36 questionnaire were assessed using a mixed model for repeated measures (time,
group, time × group). Numbers of transfusions at 3 months and 6 months were compared between groups with an analysis-of-variance test (or Kruskal-Wallis test in the case of nonnormality). Missing data were not replaced. A 2-tailed P < .05 was used to identify statistical significance. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc).

For the safety analysis, the number of related and graded adverse events was counted for each group. For the interim analysis, these characteristics were presented for the 4 groups of patients.

The interim and final statistical analysis plans are available in Supplement 2 and Supplement 3.

### Results

#### Trial Population

Eighty patients were randomized between April 2014 and January 2015 and analyzed at interim analysis in 4 groups (25-mg doses [n = 20], 50-mg doses [n = 20], and 75-mg doses [n = 19] of bevacizumab and placebo [n = 21]) in 5 different centers (Lyon, Paris Hôpital Ambroise Paré, Montpellier, Poitiers, and Marseille). The baseline characteristics are summarized in Table 1 and were similar in the 4 groups. The mean age was 60.47 (SD, 10.61) years; 37 participants (46.25%) were women. All individuals assessed for eligibility met the inclusion criteria and were enrolled in the study. The study involvement of 5 patients was terminated early because of a missing epistaxis grid at 6 months (n = 1), surgical nasal treatment (n = 1), or loss to follow-up (n = 3) (Figure 1). All patients except 1 in the bevacizumab 25-mg group completed 4 weeks of treatment and received the 3 doses of treatment. No dose-limiting toxic effects were observed.

#### Response to Treatment

**Primary Outcome at Intermediate Analysis**

Data on all patients were analyzed (n = 80). The results of the intermediate analysis are summarized in Table 2 and Figure 2. No statistical difference was observed in the placebo group compared with the other groups, regardless of dose group (P = .57). The mean duration of epistaxis after treatment was 200.4 minutes (95% CI, 109.3-291.5 minutes).

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### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bevacizumab Groups</th>
<th>Placebo Group</th>
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<tbody>
<tr>
<td></td>
<td>25 mg (n = 20)</td>
<td>50 mg (n = 20)</td>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>57.60 (10.96)</td>
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<tr>
<td></td>
<td>Median (range)</td>
<td>59.6 (39.6-76)</td>
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<tr>
<td>Female, No. (%)</td>
<td>8 (40)</td>
<td>9 (45)</td>
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<td>Mutated gene, No. (%)</td>
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<td></td>
</tr>
<tr>
<td>ALK1</td>
<td>13 (65)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>ENG</td>
<td>7 (35)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>SMAD4</td>
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<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Blood transfusions during 3 mo prior</td>
<td>5 (25)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>to inclusion, No. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Nasal surgery, No. (%)</td>
<td>10 (50)</td>
<td>10 (50)</td>
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<tr>
<td>Nasal septum perforation, No. (%)</td>
<td>3 (16)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Nasal obstruction, No. (%)</td>
<td>10 (50)</td>
<td>10 (50)</td>
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<tr>
<td>Hemoglobin level, g/dL</td>
<td>Mean (SD)</td>
<td>12.46 (2.44)</td>
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<td></td>
<td>Median (range)</td>
<td>12.8 (6.7-16.2)</td>
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<tr>
<td>Ferritin level, mg/mL</td>
<td>Mean (SD)</td>
<td>70.47 (172.58)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>19 (3-771)</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>Mean (SD)</td>
<td>138.10 (112-172)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>137.5 (112-172)</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>Mean (SD)</td>
<td>83.50 (11.32)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>81.5 (67-106)</td>
</tr>
<tr>
<td>Monthly No. of epistaxis episodes</td>
<td>Mean (SD)</td>
<td>30.99 (18.45)</td>
</tr>
<tr>
<td>during 3 mo prior to inclusion</td>
<td>Median (range)</td>
<td>32.35 (3.3-75)</td>
</tr>
</tbody>
</table>

* Nasal obstruction was self-evaluated by patients.
in the placebo group, 259.2 minutes (95% CI, 82.1-436.3 minutes) in the 25-mg bevacizumab group, 244.0 minutes (95% CI, 81.8-406.2 minutes) in the 50-mg bevacizumab group, and 215.0 minutes (95% CI, 102.8-327.2 minutes) in the 75-mg bevacizumab group. The observed difference in the mean logarithm of mean epistaxis duration was 0.26

### Table 2. Main Outcome (N = 80) 3 Months After End of Treatment: Efficacy of Bevacizumab Nasal Spray on Mean Epistaxis Duration

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
<th>Epistaxis Duration, min/mo&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Log Mean (SD) [95% CI]</th>
<th>Comparison vs Placebo, Log Mean Difference (SD) [95% CI]</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
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<tr>
<td>Before treatment</td>
<td>21</td>
<td>262.8 (230.4) [157.9-367.7]</td>
<td>212.1 (19.9-873.9)</td>
<td>5.18 (0.97) [4.95-5.43]</td>
<td></td>
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<tr>
<td>After treatment</td>
<td>21</td>
<td>200.4 (201.4) [109.3-291.5]</td>
<td>149.0 (1-660.1)</td>
<td>4.57 (1.61) [3.83-5.30]</td>
<td></td>
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<tr>
<td><strong>Bevacizumab</strong></td>
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<tr>
<td>25 mg</td>
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<tr>
<td>Before treatment</td>
<td>20</td>
<td>285.5 (433.4) [82.6-488.3]</td>
<td>199.8 (20.5-1944.9)</td>
<td>4.98 (1.16) [4.7-5.28]</td>
<td>0.26 (0.47) [-0.65 to 1.17]</td>
</tr>
<tr>
<td>After treatment</td>
<td>20</td>
<td>259.2 (378.4) [82.1-436.3]</td>
<td>163.7 (3.3-1706.9)</td>
<td>4.83 (1.36) [4.19-5.46]</td>
<td></td>
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<tr>
<td>50 mg</td>
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<tr>
<td>Before treatment</td>
<td>20</td>
<td>229.0 (215.9) [128-330]</td>
<td>140.6 (33.4-754.4)</td>
<td>5.03 (0.93) [4.79-5.27]</td>
<td>0.26 (0.45) [-0.63 to 1.15]</td>
</tr>
<tr>
<td>After treatment</td>
<td>20</td>
<td>244.0 (346.6) [81.8-406.2]</td>
<td>140.8 (7.6-1592.2)</td>
<td>4.83 (1.28) [4.23-5.43]</td>
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<tr>
<td>75 mg</td>
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<tr>
<td>Before treatment</td>
<td>19</td>
<td>272.9 (396.6) [81.7-464]</td>
<td>159.5 (29.0-1739.4)</td>
<td>5.02 (1.05) [4.75-5.3]</td>
<td>0.20 (0.46) [-0.70 to 1.10]</td>
</tr>
<tr>
<td>After treatment</td>
<td>19</td>
<td>215.0 (232.8) [102.8-327.2]</td>
<td>147.0 (8.4-969.8)</td>
<td>4.77 (1.28) [4.15-5.38]</td>
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</tbody>
</table>

<sup>a</sup> Mean epistaxis duration before treatment was measured in the 3 consecutive months before treatment. Mean epistaxis duration after treatment was measured in the 3 consecutive months after treatment (from day 29 to day 118).

<sup>b</sup> P value for comparison of each group with placebo (by t test) at end of treatment.
(95% CI, −0.65 to 1.17) in the 25-mg bevacizumab group, 0.26 (95% CI, −0.63 to 1.15) in the 50-mg bevacizumab group, and 0.20 (95% CI, −0.70 to 1.10) in the 75-mg bevacizumab group. The primary outcome showed higher variability than originally considered in the protocol, with a standard deviation twice that used when planning the trial. On the basis of these results and after meeting with the independent data monitoring committee, the investigators decided to stop the study.

Secondary Outcomes

At 3 and 6 months after the end of the treatment, no significant differences were observed between the bevacizumab and placebo groups in terms of the number of epistaxis episodes ($P = .55$) (Figure 3A). The mean numbers of epistaxis episodes before treatment (from day −90 to day −1) and 3 months after treatment (from day 29 to day 118), respectively, were 30.99 vs 23.13 in the 25-mg bevacizumab group, 25.06 vs 20.01 in the 50-mg bevacizumab group, 27.84 vs 24.35 in the 75-mg bevacizumab group, and 31.37 vs 24.27 in the placebo group ($P = .24$).

The number of red blood cell transfusions did not differ significantly from inclusion to 3 and 6 months after the end of the treatment ($P = .35$ and $P = .39$, respectively). Mean numbers of red blood cell transfusions were 0.15 and 0.25 in the 25-mg bevacizumab group, 1.45 and 2.40 in the 50-mg group, 1.16 and 1.79 in the 75-mg group, and 0.76 and 1.05 in the placebo group from inclusion to 3 and 6 months after the end of the treatment, respectively.

Biological criteria (hemoglobin level [Figure 3B] and ferritin level) were not significantly improved 3 and 6 months after the end of the treatment. Mean hemoglobin level did not significantly improve over time ($P = .66$) and evolution was not different between groups ($P = .68$). Values at inclusion, month 3, and month 6, respectively, were 11.46 g/dL, 11.28 g/dL in the 75-mL group; and 12.25 g/dL, 12.34 g/dL, and 12.42 g/dL in the placebo group.

Mean ferritin levels at inclusion, month 3, and month 6, respectively, were 70.47 μg/L, 50.55 μg/L, and 64.63 μg/L in the 25-mg group; 42.55 μg/L, 40.10 μg/L, and 44.47 μg/L in the 50-mg group; 52.21 μg/L, 59.53 μg/L, and 33.53 μg/L in the 75-mg group; and 86.00 μg/L, 78.62 μg/L, and 53.42 μg/L in the placebo group. There was no significant trend over time ($P = .86$) and no difference of evolution between groups was observed ($P = .70$).

The SF-36 questionnaire (Figure 3, C and D) revealed no differences in the dimensions of quality of life after treatment (bodily pain, $P = .71$; general health, $P = .97$; mental health, $P = .59$; physical functioning, $P = .68$; social functioning, $P = .66$; and vitality, $P = .67$); it did find differences in 2 dimensions (emotional role, $P = .008$; and physical role, $P = .006$). There were no differences in evolution between the groups.

Safety Outcomes

No adverse events certainly or probably related to the treatment were recorded. A total of 161 adverse events were recorded without differences between the groups (47 in the 25-mg bevacizumab group, 33 in the 50-mg bevacizumab group, 38 in the 75-mg bevacizumab group, and 43 in the placebo group). Of these, 26 unrelated serious adverse events (classified into 37 different system organ classes) were observed (9 in the 25-mg group, 5 in the 50-mg group, 6 in the 75-mg group, and 6 in the placebo group). No blood pressure variation was recorded before or after treatment.

Discussion

This phase 2, double-blind, multicenter, randomized, placebo-controlled trial examined the efficacy of intranasal
bevacizumab spray for epistaxis in patients with HHT. None of 25-, 50-, or 75-mg doses of bevacizumab per treatment, administered as a nasal spray with a total of 3 sprays every 14 days for 1 month, reduced epistaxis duration in HHT patients compared with placebo. Treatment with bevacizumab had no measurable effect on secondary outcomes,

Figure 3. Secondary Outcome Criteria Before and After Treatment in Each Group

A No. of epistaxis episodes per month

B Hemoglobin level

C SF-36 physical component score

D SF-36 mental component score

Error bars indicate 95% CIs. SF-36 indicates Short Form Health Survey quality-of-life questionnaire.
including number of epistaxis episodes, quality of life, number of red blood cell transfusions, or hemoglobin and ferritin levels. We previously published the results of a phase 1 study that did not show any efficacy. In that case, however, the spray was administered only once to assess tolerance.13 Riss and colleagues18 published encouraging results for nasal bevacizumab in 9 patients, although the drug (100 mg of bevacizumab) was injected into the nasal mucosa under endoscopic control. To avoid the risk of nasal septum perforation, we preferred to use a nasal spray. Many of the case reports published support the possible efficacy of a bevacizumab nasal spray.9,11,19-21 However, because of high variation in the number and duration of epistaxis episodes in patients with HHT, prospective randomized clinical trials are needed to definitively determine efficacy of any proposed intervention.

The absence of observed efficacy for intranasal bevacizumab might be related to several factors. First, bevacizumab is a recombinant, humanized, IgG1 monoclonal antibody with a high molecular weight (149 kDa), a characteristic that may limit transport through biological membranes. We previously performed an ex vivo study to assess its transport through the nasal mucosa.7 The bevacizumab concentrations found in the mucosa were highly variable, ranging from 6% to 42% depending on the sample and its localization (cavity or septum). We can thus hypothesize that bevacizumab absorption varies considerably for each patient and within a single patient. Frequent nosebleeds and nasal crust are also a physical barrier to drug absorption. This was reinforced by the pharmacokinetics analysis performed in the phase 1 study, showing that the drug was not detected in any blood samples.13 Second, the doses and administration of bevacizumab may have been inadequate. However, dosing was based on previous case reports suggesting efficacy: 1 mg into each nostril twice each day for 2 consecutive weeks9 or with higher doses 1 time in a repeated manner (25 mg into each nostril,9 100 mg every 8 to 9 weeks,19 and 50 mg initiated at the request of the patient after a new increase in the Epistaxis Severity Score).20

Tolerance of intranasal bevacizumab was excellent after a 1-day nasal spray administration 3 times, regardless of the dose. As in other cases published using intranasal bevacizumab alone, no treatment-related adverse events were observed.9,20,22 Patients were carefully monitored for nasal cartilaginous septum perforations, which have been described as an adverse effect of intravenous bevacizumab in cancer patients,23-26 as well as submucosal bevacizumab injections11,21 or laser treatments,27 but never topical treatments. In this study, nasal cartilaginous septum perforation was not observed following treatment administration. No pharmacokinetics study was performed for this study, but no systemic effect was in evidence. No variations in blood pressure were observed.

This trial had several limitations. First, patients completed epistaxis grids and noted epistaxis duration, which are not directly observed outcomes and are subject to error. In other countries, the Epistaxis Severity Score is used, taking into account epistaxis frequency and duration and blood transfusions. The present study used the same tool (the epistaxis grid) as in previous published studies on epistaxis in HHT.6,13,17 Second, we included all HHT patients with nosebleeds and did not take into account a history of nasal surgery or nasal crusts, which may change mucosal drug absorption. Almost all patients had undergone different types of surgery. Third, early termination of the study after the first stage is a limitation. The principle of nonbinding termination for futility was envisaged in the protocol. We acknowledge that the decision to stop the trial was crucial. It followed the recommendations of the independent data monitoring committee. In this study, the observed effect was consistent in the 3 groups, but in the opposite direction to that expected (a worse outcome for the 3 bevacizumab groups compared with placebo). It is possible that a real effect was missed, as the study was powered based on the assumption of a large effect size (40%). Moreover, the primary outcome showed higher variability than originally considered in the protocol, with a standard deviation twice that used when planning the trial. Independent statistical analysis provided the independent data monitoring committee with conditional power calculations, which showed that, accounting for this higher variability, the trial had a low probability of concluding if it continued to the second stage, even when increasing the sample size within the limits fixed by the protocol.

Conclusions

In patients with HHT, a bevacizumab nasal spray treatment of 3 administrations at 14-day intervals with doses of 25 mg, 50 mg, or 75 mg per spray, compared with a placebo, did not reduce monthly epistaxis duration in the 3 consecutive months immediately after the end of treatment.
responsible for the integrity of the data and the accuracy of the data analysis.

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